Remarks/Arguments

I. Status of the Claims:

Claims 141, 150, 155-159 and 162-173 stand rejected. Claims 141, 150, 155, 156, 166 and 169 are presently amended. Claims 141, 150, 155-159 and 161-173 are pending in the case.

II. Rejections Under 35 U.S.C. § 112:

Claim 173 stands rejected under 35 U.S.C. §112 for allegedly lacking antecedent basis for the claim element "highlight fragment". Claim 169 has been amended to recite, in part "i) wherein the nucleic acid ladder further comprises at least one highlight fragment having a size in the range of 100 base pairs to 5 kilobase pairs and having a relative mass that is three times greater than the relative mass of other molecules in the composition, or; ii) wherein at least one of the three or more molecules is a highlight fragment having a relative mass that is three times greater than the relative mass of the other molecules in the composition".

In light of the amendment made above, Applicant respectfully submits that claim 173 is in compliance with the requirements set forth in 35 USC §112, second paragraph, and respectfully requests that the rejection thereof on these grounds be removed.

III. Rejections Under 35 U.S.C. § 103:

Claims 141, 150, 155-157, 159 and 162-164 stand rejected under 35 USC §103(a) as allegedly being obvious over U.S. patent no. 5,316,908 to Carlson, *et al*. (hereinafter "Carlson") or Stratagene 1993 or Stratagene Catalog 1993.

The Examiner states "[f]or purposes of examination, the claims have been construed as encompassing not only the explicitly recited nucleic acid fragments/bands, as well as any number and combinations of additional ingredients, including alternative bands, so long as they do not affect the claimed nucleic acid fragments (t)hat go to form the claimed ladder" (Office action, Page 4, section 10) and asserts that Fig. 1 of Carlson discloses "multiple nucleic acid fragments that have the same intensity". Applicant respectfully disagrees with these rejections and submits that the interpretation of Carlson's Fig. 1 is incorrect for at least the following reasons. First, Fig. 1 of Carlson is not photographic representation

of the DNA markers that are disclosed. Instead, Fig. 1 is a "schematic, scale drawing of how the first and second molecular markers **would migrate** on an electrophoresis gel" (Carlson, Col. 2, lines 21-23; *Emphasis added*). A schematic drawing, by its very definition, represents elements of a system (e.g., band of a molecular weight ladder) using abstract, graphic symbols rather than realistic pictures. A schematic usually omits all details that are not relevant to the information the schematic is intended to convey, and may even add unrealistic elements that aid comprehension (http://en.wikipedia.org/wiki/Schematic).

Carlson's Fig. 1 is a schematic drawing and Carlson only provided information relating to the size of each band in base pairs, and how each band would *migrate* in a gel when subjected to an electromotive force. The drawing is meant to convey information relating to electrophoretic *migration* of the individual bands through a gel. There is nothing in Fig. 1 or in any of Carlson's disclosure that relates to or conveys any information about the *mass* of DNA in individual bands, as defined in the instant claims, because Carlson was not trying to convey any information about the *relative mass* of the bands forming his nucleic acid markers.

The Exmainer further states "At page 13 of the response applicant asserts that Carlson et al., do not reach adjusting the relative number ofthe various DNA fragments so as to have the same relative mass. This argument ahs been considered and has not been found persuasive. While Carlson et al., may teach alternative embodiments, there can be no doubt that the bands represented in FIG. 1 do have the same relative intensity, ergo, the same relative mass. Argument is also presented that the DNA fragments were derived from a particular source. This argument has not been found persuasive, as the claims at hand recite no restriction as to the source ofthe DNA and/or RNA" (Office action, page 13, sections 31 and 32). The Examiner therefore appears to have entirely ignored Applicant's argument demonstrating that the very methods used by Carlson to make the disclosed marker contradict the Examiner's interpretation of the Carlson reference. Applicant respectfully submits that it is improper to extrapolate information relating to the **mass** of individual bands using Fig.1, since the intent thereof was to represent band migration (i.e., band size), not mass (i.e., DNA content). As previously discussed, the very nature by which Carlson's DNA markers are made (i.e., by pooling restriction digests of a single larger λ-page DNA) will not result in a DNA marker ladder shown in Fig. 1. Carlson clearly states "[t]he ladder is made up of pooled DNA restriction endonuclease digests" (Abstract). Carlson further states "[t]o make a restriction digest, λ-DNA was digested with one or two restriction endonucleases. The enzymes used for individual digests are indicated in Tables 2 and 3. Digestions were performed under standard conditions,

generally according to the instructions of the enzyme's manufacturer. Restriction digests were pooled after digestion" (Carlson, Col. 4, lines 58 – 64).

Asplicant has stated previously, if each band depicted in Carlson's Fig. 1 were of equal intensity, as the Examiner claims, then the copy number of each of the bands would have to have been adjusted to compensate for the decrease in DNA mass for each progressively smaller band. In other words, the only way that a band that is smaller in size than a reference band can have an equal intensity to the reference band when stained with ethidium bromide is if the copy number of the smaller band were increased sufficiently to compensate for the decrease in DNA mass in the smaller band. There is nothing in Carlson to indicate that the copy number of any of the bands was altered to ensure that each band was visualized with equal intensity. Instead, Carlson's bands are made by pooling individual restriction digests of λ-DNA, which means that the DNA in each band is present in an equimolar ratio (i.e., assuming complete digestion of the λ-page DNA, mole equivalent of each of the resulting bands is 1:1…:1). There is no indication or suggestion in Carlson that the copy number of any band was adjusted so that the bands would show up on an electrophoresis gel with equal intensity when stained with ethidium bromide. In fact, in Example 2 (First Marker Kit), Carlson explicitly states "[i]n the first ladder, the target DNA consisted of pooled *equal* amounts of 31 different restriction digests of phage λ DNA" (Carlson, Col. 4, last sentence; Emphasis added). If the input λ DNA of each digest was equal, as Carlson states, then each band should be visualized with its appropriate mass intensity, which was not adjusted. Yet, the intensity of each band constituting the molecular weight marker on the left side of Fig. 1 is equal, reinforcing Applicant's point that Fig. 1 is not a realistic representation of Carlson's marker set. In fact, the only indication that Carlson adjusted the amount of any of the individual bands in the marker set is found in Example 3: Second Marker Kit, which states in part "[t]he third improvement was to increase the amounts, i.e. relative copy number or the dosage, of the target DNA for the largest and smallest bands. Large DNA fragments blot inefficiently. As is well known in the art, small fragments are retained on membranes poorly during hybridization. Therefore, the signal from large DNA fragments and small DNA fragments tends to be less than the signal from bands in the middle range. This improvement compensated for that effect" (Carlson, Col. 5, lines 55-60). Table 3 (Carlson, Col. 7) outlines the size of each DNA fragment appearing on the right hand side of Fig. 1, along with its dosage compensation (either 3 or 1). According to Table 3, the smallest 526 bp fragment and the largest 22.6 kb fragment are present in equimolar amounts (i.e., 3-fold), which means that the 22.6 kb band contains 43-fold as on a DNA on mass basis as the 526 bp band, yet both bands are represented with equal intensity in Fig. 1. Additionally,

if the 6.4 kb Ava II band is compared with the 5.8 kb Hae II band, both of which are similar to each other in size and which are depicted in Fig. 1 as bands with equal intensity, we see that the 6.4 kB Ava II band actually has 3.3-fold the amount (i.e., mass) DNA present in the 5.8 kb Hae II band (i.e., compare the 3 fold dose of the 6.4 kb band with the 1-fold dose of the 5.8 kb band). Despite this large differential in the actual amount of DNA present in each band, Carlson depicts the bands as having equal intensity in Fig. 1. Similarly, the 910 bp Eco RV/Bam HI band is compared with the 784 bp Dde I band, both of which are similar in size and which are depicted in Fig. 1 as bands with equal intensity, we see that the smaller 784 bp Dde I band actually has 2.6-fold the amount (i.e., mass) of DNA as the larger 910 bp Eco RV/Bam HI band (i.e., compare the 3 fold dose of the Dde I band with the 1-fold dose of the Eco RV/Bam HI band). The above serves to illustrate the fact that there is no correlation between the size, mass or relative mass and the depicted band intensity of the fragments shown in Carlson's Fig. 1, and no conclusion about same can be made.

The Examiner has not addressed the seeming incongruence between his interpretation of Fig. 1 and the very nature of the DNA marker produced by Carlson using the methods described therein (i.e., pooling individual restriction digests of λ-DNA). Instead, the Examiner simply dismisses Applicant's argument (which is based on the very disclosure being cited against the claims) by repeating the assertion that "[t]his argument has been considered and has not been found persuasive. While Carlson et al., may teach alternative embodiments, there can be no doubt that the bands represented in FIG. 1 do have the same relative intensity, ergo, the same relative mass" (Office action, section 31). If the Examiner insists that the bands in Carlson's Fig. 1 have equal intensity in real life, as it appears he is doing and despite direct written evidence in Carlson's disclosure to the contrary, then Applicant respectfully requests that in accordance with MPEP 2144.03, the Examiner please provide a sworn statement of fact explicitly setting forth the scientific/technical basis upon which the assertion is being made that a DNA marker made up of pooled DNA restriction endonuclease digests according to Carlson's teachings can have bands of equal intensity when visualized by ethidium bromide staining without having to alter the copy number of smaller DNA fragments to compensate for the reduced mass of DNA in smaller bands. Otherwise, Applicant maintains the position, based on the arguments already made of record, that the prior art references fail to establish a *prima facie* case of obviousness against the claims.

In light of the arguments presented above, and by the Examiner's own statements, Applicant respectfully submits that Carlson fails to establish a *prima facie* case of obviousness against the instant claims. Neither of the two Stratagene references remedies this deficiency since they fail to address the

incorrect interpretation of Carlson's schematic depiction of the bands. Accordingly, Applicant submits that claims 141, 150, 155-157, 159, and 162-173 are unobvious and patentable over the Carlson and Stratagene references, taken alone or in combination and respectfully requests the rejections under 35 USC 103(a) be withdrawn.

CONCLUSION

The extendable due date for filing an Appeal Brief/Response to the most recent Office Action, under a two-month shortened statutory period, is **January 17, 2011**. Applicants therefore hereby petition for a **three (3)-month extension** of time under 37 C.F.R. § 1.136(a), thereby extending the due date for response to **April 17, 2011**. In association therewith, Applicants hereby authorize the Commissioner to charge Deposit Account No. 50-3994 in the amount of **$1,100.00**, the fee set forth under 37 C.F.R. § 1.17(a)(3). Applicants do not believe that any additional fees are due in connection with the filing of this paper. However, in the unlikely event that any such fees are due, the Commissioner is hereby authorized to charge the same to Deposit Account No. 50-3994, with reference to our matter IVGN 187.1 CON.

Respectfully submitted,

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